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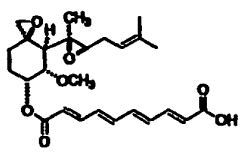
(54) Title: TYPE 2 METHIONINE AMINOPEPTIDASE (MetAP2) INHIBITORS AND USES THEROF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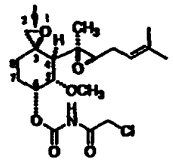
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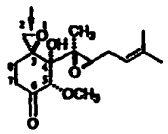
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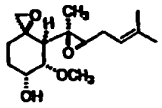
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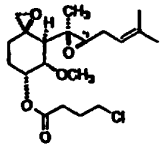
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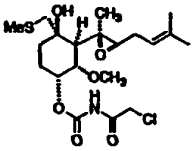
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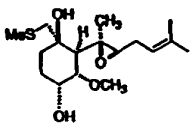
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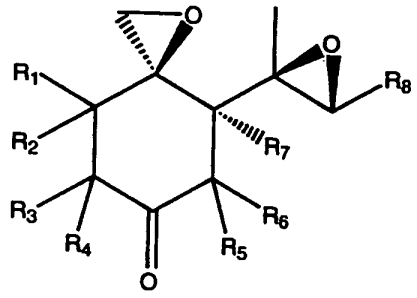
(57) Abstract

Novel compounds that are anti-angiogenic or immunosuppressive are described. Also described are methods for determining if an animal is at risk for a disease involving abnormal angiogenesis or an immune reaction resulting in pathology comprising evaluating an aspect of MetAP2 metabolism or structure; methods for identifying agents that are anti-angiogenic or immunosuppressive comprising evaluating the effect of the agent on an aspect of MetAP2 metabolism; methods for treating a cell having an abnormality in metabolism or structure of MetAP2; and methods for treating abnormal angiogenesis or an immune reaction which results in pathology in an animal. Pharmaceutical compositions are also provided.

CLAIMS

1. A compound of the formula:



(I)

and pharmaceutically acceptable salts thereof,

wherein

R_1, R_2, R_3, R_4, R_5 and R_6 can be the same or different from each other, and are hydrogen, alkyl, aryl, halogen, hydroxyl, alkoxy, carbamoyl, carbonyldioxyl, thiohydroxyl, amino, alkylamino, dialkylamino, ureido, lower alkoxy, a substituted alkanoyl group, a cyclic or aromatic cyclic group which can be optionally substituted, a heterocyclic or aromatic heterocyclic group which can be optionally substituted, a substituted aryl or aroyl group having at least one substituent selected from the group consisting of alkyl, amino, halogen, hydroxyl, lower alkoxy, cyano, amide, carbamoyl, carboxylic acid, carboxyl ester, carboxyl salt, hydroxyl and alkylthioether;

R_7 is hydrogen or an hydroxy group; and

R_8 is

(1) a subtituted alkyl, allyl or alkyne group; or

(2) a substituted alkoxyl or thioalkoxyl group, or methylene or ethylene alkoxyl or thioalkoxyl group, wherein the methylene or ethylene can be optionally substituted; or

(3) an aroyl group which can be optionally substituted with at least one substituent selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halogen, hydroxyl, lower alkoxy, cyano, amido, carbamoyl, thiocarbamoyl, carbonyldioxyl, carboxylic acid, carboxyl ester, carboxyl salt, alkyl or dialkylcarbamoyl, substituted ureido, vinyl, cyclic or aromatic cyclic groups which can be optionally substituted, or a heterocyclic or aromatic heterocyclic group which can be optionally substituted; or

(4) an aryl group which can be optionally substituted with at least one substituent selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halogen, hydroxyl, lower alkoxy, cyano, amido, carbamoyl, thiocarbamoyl, carbonyldioxyl, carboxylic acid, carboxyl ester, carboxyl salt, alkyl or dialkylcarbamoyl, substituted ureido, vinyl, cyclic or aromatic cyclic groups which can be optionally substituted, or a heterocyclic or aromatic heterocyclic group which can be optionally substituted; or

(5) an amino, alkylamino, dialkylamino, halogen, hydroxyl, cyano, amido, carbamoyl, thiocarbamoyl, carbonyldioxyl, carboxyl, alkyl, dialkylcarbamoyl, ureido, vinyl, cyclic or aromatic cyclic groups which can be optionally substituted, a heterocyclic or aromatic heterocyclic group which can be optionally substituted, carboxylic acid, carboxyl ester, carboxyl salt; or

(6) an alkyl group which can be optionally substituted with $N^+P_1P_2P_3X^-$ or $S^+P_1P_2X^-$, wherein P_1, P_2 and P_3 can be the same or different and are each an optionally substituted hydrocarbon or heterocyclic group and X^- is a counter anion; or

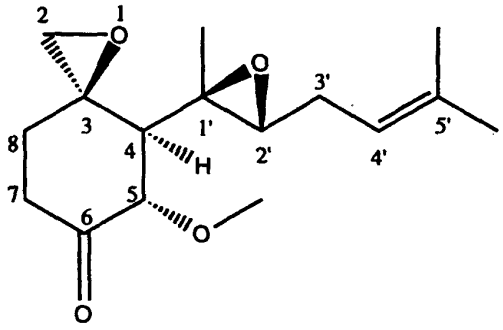
(7) 2-methyl-1-propenyl or an isobutyl group which can be optionally substituted with hydroxyl, carbamoyl, carbonyldioxyl, thiohydroxyl, amino, alkylamino, dialkylamino, ureido, alky, lower alkoxy, a substituted alkanoyl group, a cyclic or aromatic cyclic group which can be optionally substituted, a heterocyclic or aromatic heterocyclic group which can be optionally substituted, a substituted aryl or aroyl group having at least one substituent selected from the group consisting of alkyl, amino, halogen, hydroxyl, lower alkoxy, cyano, amide, carbamoyl, carboxylic acid, carboxyl ester, carboxyl salt, hydroxyl or alkylthioether; or

(8) 2-methyl-1-propenyl or an isobutyl group which can be optionally substituted with $N^+P_1P_2P_3X^-$, $S^+P_1P_2X^-$, wherein P_1, P_2 and P_3 can be the same or different and are each an optionally substituted hydrocarbon or heterocyclic group and X^- is a counter anion; or

(9) a benzenesulfonyl, methylsulfonyl or alkyl sufonyl group, with or without a methylene or ethylene substituent, or the corresponding amide or ester, which can be optionally substituted; or

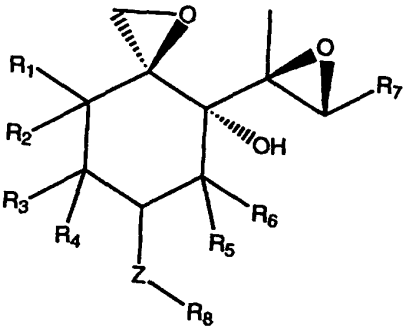
(10) an alkoxycarbonyl or phenoxycarbonyl group with or without a methylene or ethylene substituent, which can be optionally substituted.

2. A compound according to claim 1 wherein the formula is:



(I)

3. A compound of the formula:



(II)

and pharmaceutically acceptable salts thereof,

wherein

Z is an oxygen and can have R or S configuration;

R_1, R_2, R_3, R_4, R_5 and R_6 can be the same or different from each other and are hydrogen, alkyl, aryl, halogen, hydroxyl, alkoxy, carbamoyl, carbonyldioxyl, thiohydroxyl, amino, alkylamino, dialkylamino, ureido, lower alkoxy, a substituted alkanoyl group, a cyclic or aromatic cyclic group which can be optionally substituted, a heterocyclic or aromatic heterocyclic group which can be optionally substituted, a substituted aryl or aroyl group having at least one substituent selected from the group consisting of alkyl, amino, halogen, hydroxyl, lower alkoxy, cyano, amide, carbamoyl, carboxylic acid, carboxyl ester, carboxyl salt, hydroxyl and alkylthioether;

R_7 and R_8 can be the same or different from each other and are:

(1) hydrogen or a subtituted alkyl, allyl or alkyne group;

(2) a substituted alkoxyl or thioalkoxyl group, or methylene or ethylene alkoxyl or thioalkoxyl group, wherein the methylene or ethylene can be optionally substituted;

(3) an aroyl group which can be optionally substituted with at least one substituent selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halogen, hydroxyl, lower alkoxy, cyano, amido, carbamoyl, thiocarbamoyl, carbonyldioxyl, carboxylic acid, carboxyl ester, carboxyl salt, alkyl or dialkylcarbamoyl, substituted ureido, vinyl, cyclic or aromatic cyclic groups which can be optionally substituted, or a heterocyclic or aromatic heterocyclic group which can be optionally substituted; or

(4) an aryl group which can be optionally substituted with at least one substituent selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halogen, hydroxyl, lower alkoxy, cyano, amido, carbamoyl, thiocarbamoyl, carbonyldioxyl, carboxylic acid, carboxyl ester, carboxyl salt, alkyl or dialkylcarbamoyl, substituted ureido, vinyl, cyclic or aromatic cyclic groups which can be optionally substituted, or a heterocyclic or aromatic heterocyclic group which can be optionally substituted; or

(5) an amino, alkylamino, dialkylamino, halogen, hydroxyl, cyano, amido, carbamoyl, thiocarbamoyl, carbonyldioxyl, carboxyl, alkyl, dialkylcarbamoyl, ureido, vinyl, cyclic or aromatic cyclic groups which can be optionally substituted, a heterocyclic or aromatic heterocyclic group which can be optionally substituted, carboxylic acid, carboxyl ester, carboxyl salt; or

(6) an alkyl group which can be optionally substituted with $N^+P_1P_2P_3X^-$, $S^+P_1P_2X^-$, wherein P_1, P_2 and P_3 can be the same or different and are each an optionally substituted hydrocarbon or heterocyclic group and X^- is a counter anion; or

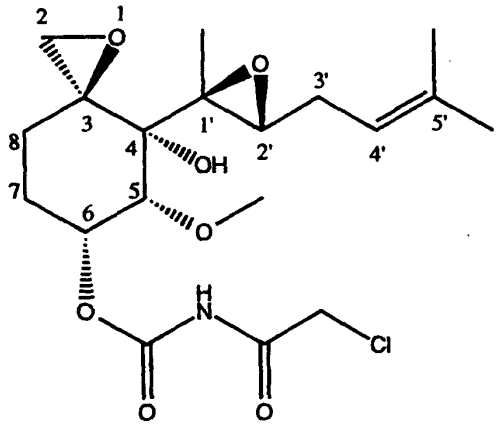
(7) 2-methyl-1-propenyl or an isobutyl group which can be optionally substituted with hydroxyl, carbamoyl, carbonyldioxyl, thiohydroxyl, amino, alkylamino, dialkylamino, ureido, alky, lower alkoxy, a substituted alkanoyl group, a cyclic or aromatic cyclic group which can be optionally substituted, a heterocyclic or aromatic heterocyclic group which can be optionally substituted, a substituted aryl or aroyl group having at least one substituent selected from the group consisting of alkyl, amino, halogen, hydroxyl, lower alkoxy, cyano, amide, carbamoyl, carboxylic acid, carboxyl ester, carboxyl salt, hydroxyl or alkylthioether;

(8) 2-methyl-1-propenyl or an isobutyl group which can be optionally substituted with $N^+P_1P_2P_3X^-$, $S^+P_1P_2X^-$, wherein P_1, P_2 and P_3 can be the same or different and are each an optionally substituted hydrocarbon or heterocyclic group and X^- is a counter anion; or

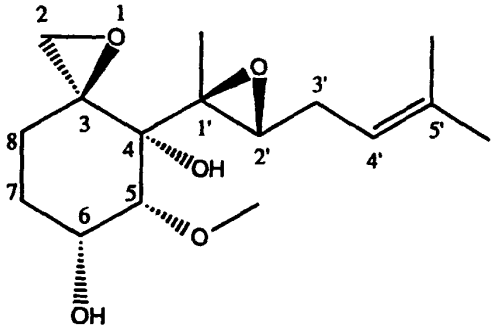
(9) a benzenesulfonyl, methylsulfonyl or alkyl sufonyl group, with or without a methylene or ethylene substituent, or the corresponding amide or ester, which can be optionally substituted; or

(10) an alkoxycarbonyl or phenoxycarbonyl group with or without a methylene or ethylene substituent, which can be optionally substituted.

4. A compound according to claim 3 wherein the formula is selected from the group consisting of:

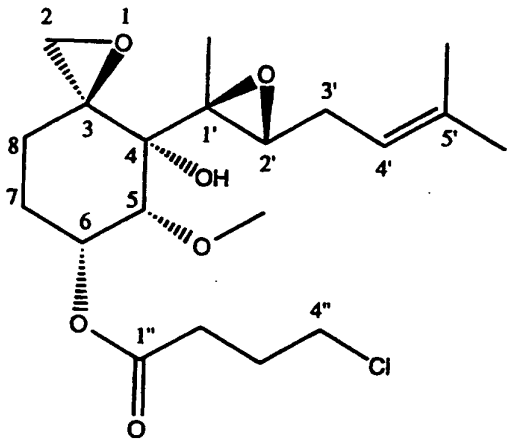


(2)



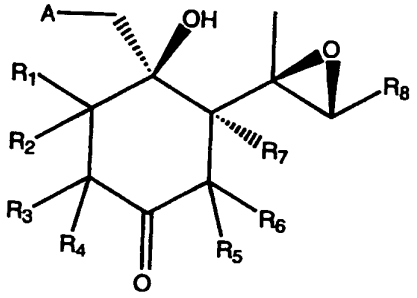
(3)

and



(4)

5. A compound of the formula:



(III)

and pharmaceutically acceptable salts thereof,

wherein

A is a halogen, $N^+P_1P_2P_3X^-$ or $S^+P_1P_2X^-$, wherein P_1, P_2 and P_3 can be the same or different and are each an optionally substituted hydrocarbon or heterocyclic group and X^- is a counter anion;

R_1, R_2, R_3, R_4, R_5 and R_6 can be the same or different from each other, and are hydrogen, alkyl, aryl, halogen, hydroxyl, alkoxy, carbamoyl, carbonyldioxyl, thiohydroxyl, amino, alkylamino, dialkylamino, ureido, lower alkoxy, a substituted alkanoyl group, a cyclic or aromatic cyclic group which can be optionally substituted, a heterocyclic or aromatic heterocyclic group which can be optionally substituted, a substituted aryl or aroyl group having at least one substituent selected from the group consisting of alkyl, amino, halogen, hydroxyl, lower alkoxy, cyano, amide, carbamoyl, carboxylic acid, carboxyl ester, carboxyl salt, hydroxyl and alkylthioether;

R_7 is hydrogen or an hydroxy group; and

R_8 is

(1) a subtituted alkyl, allyl or alkyne group; or

(2) a substituted alkoxyl or thioalkoxyl group, or methylene or ethylene alkoxyl or thioalkoxyl group, wherein the methylene or ethylene can be optionally substituted; or

(3) an aroyl group which can be optionally substituted with at least one substituent selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halogen, hydroxyl, lower alkoxy, cyano, amido, carbamoyl, thiocarbamoyl, carbonyldioxyl, carboxylic acid, carboxyl ester, carboxyl salt, alkyl or dialkylcarbamoyl, substituted ureido, vinyl, cyclic or aromatic cyclic groups which can be optionally substituted, or a heterocyclic or aromatic heterocyclic group which can be optionally substituted; or

(4) an aryl group which can be optionally substituted with at least one substituent selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halogen, hydroxyl, lower alkoxy, cyano, amido, carbamoyl, thiocarbamoyl, carbonyldioxyl, carboxylic acid, carboxyl ester, carboxyl salt, alkyl or dialkylcarbamoyl, substituted ureido, vinyl, cyclic or aromatic cyclic groups which can be optionally substituted, or a heterocyclic or aromatic heterocyclic group which can be optionally substituted; or

(5) an amino, alkylamino, dialkylamino, halgen, hydroxyl, cyano, amido, carbamoyl, thiocarbamoyl, carbonyldioxyl, carboxyl, alkyl, dialkylcarbamoyl, ureido, vinyl, cyclic or aromatic cyclic groups which can be optionally substituted, a heterocyclic or aromatic heterocyclic group which can be optionally substituted, carboxylic acid, carboxyl ester or carboxyl salt; or

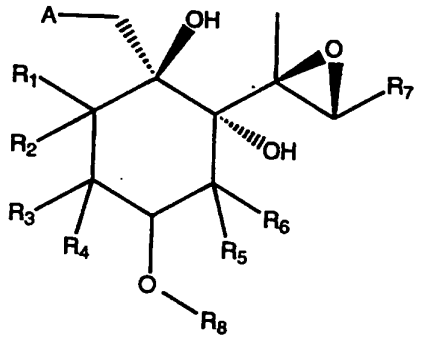
(6) 2-methyl-1-propenyl or an isobutyl group which can be optionally substituted with hydroxyl, carbamoyl, carbonyldioxyl, thiohydroxyl, amino, alkylamino, dialkylamino, ureido, alky, lower alkoxy, a substituted alkanoyl group, a cyclic or aromatic cyclic group which can be optionally substituted, a heterocyclic or aromatic heterocyclic group which can be optionally substituted, a substituted aryl or aroyl group having at least one substituent selected from the group consisting of alkyl, amino, halogen, hydroxyl, lower alkoxy, cyano, amide, carbamoyl, carboxylic acid, carboxyl ester, carboxyl salt, hydroxyl or alkylthioether; or

(7) a benzenesulfonyl, methylsulfonyl or alkyl sufonyl group, with or without a

methylene or ethylene substituent, or the corresponding amide or ester, which can be optionally substituted; or

(8) an alkoxycarbonyl or phenoxycarbonyl group with or without a methylene or ethylene substituent, which can be optionally substituted.

6. A compound of the formula:



(IV)

and pharmaceutically acceptable salts thereof,

wherein

A is a halogen, $N^+P_1P_2P_3X^-$ or $S^+P_1P_2X^-$, wherein P_1, P_2 and P_3 can be the same or different and are each an optionally substituted hydrocarbon or heterocyclic group and X- is a counter anion;

R_1, R_2, R_3, R_4, R_5 and R_6 can be the same or different from each other and are hydrogen, alkyl, aryl, halogen, hydroxyl, alkoxy, carbamoyl, carbonyldioxyl, thiohydroxyl, amino, alkylamino, dialkylamino, ureido, lower alkoxy, a substituted alkanoyl group, a cyclic or aromatic cyclic group which can be optionally substituted, a heterocyclic or aromatic heterocyclic group which can be optionally substituted, a substituted aryl or aroyl group having at least one substituent selected from the group consisting of alkyl, amino, halogen, hydroxyl, lower alkoxy, cyano, amide, carbamoyl, carboxylic acid, carboxyl ester, carboxyl salt, hydroxyl and alkylthioether;

R_7 is hydrogen or an hydroxy group; and

R_8 is:

(1) hydrogen or a subtituted alkyl, allyl or alkyne group;

(2) a substituted alkoxyl or thioalkoxyl group, or methylene or ethylene alkoxyl or

thioalkoxyl group, wherein the methylene or ethylene can be optionally substituted;

(3) an aroyl group which can be optionally substituted with at least one substituent selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halogen, hydroxyl, lower alkoxy, cyano, amido, carbamoyl, thiocarbamoyl, carbonyldioxyl, carboxylic acid, carboxyl ester, carboxyl salt, alkyl or dialkylcarbamoyl, substituted ureido, vinyl, cyclic or aromatic cyclic groups which can be optionally substituted, or a heterocyclic or aromatic heterocyclic group which can be optionally substituted; or

(4) an aryl group which can be optionally substituted with at least one substituent selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halogen, hydroxyl, lower alkoxy, cyano, amido, carbamoyl, thiocarbamoyl, carbonyldioxyl, carboxylic acid, carboxyl ester, carboxyl salt, alkyl or dialkylcarbamoyl, substituted ureido, vinyl, cyclic or aromatic cyclic groups which can be optionally substituted, or a heterocyclic or aromatic heterocyclic group which can be optionally substituted; or

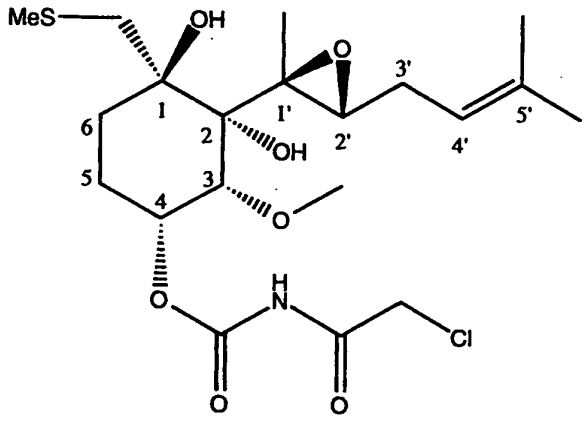
(5) an amino, alkylamino, dialkylamino, halogen, hydroxyl, cyano, amido, carbamoyl, thiocarbamoyl, carbonyldioxyl, carboxyl, alkyl, dialkylcarbamoyl, ureido, vinyl, cyclic or aromatic cyclic groups which can be optionally substituted, a heterocyclic or aromatic heterocyclic group which can be optionally substituted, carboxylic acid, carboxyl ester, carboxyl salt; or

(6) 2-methyl-1-propenyl or an isobutyl group which can be optionally substituted with hydroxyl, carbamoyl, carbonyldioxyl, thiohydroxyl, amino, alkylamino, dialkylamino, ureido, alky, lower alkoxy, a substituted alkanoyl group, a cyclic or aromatic cyclic group which can be optionally substituted, a heterocyclic or aromatic heterocyclic group which can be optionally substituted, a substituted aryl or aroyl group having at least one substituent selected from the group consisting of alkyl, amino, halogen, hydroxyl, lower alkoxy, cyano, amide, carbamoyl, carboxylic acid, carboxyl ester, carboxyl salt, hydroxyl or alkylthioether;

(7) a benzenesulfonyl, methylsulfonyl or alkyl sufonyl group, with or without a methylene or ethylene substituent, or the corresponding amide or ester, which can be optionally substituted; or

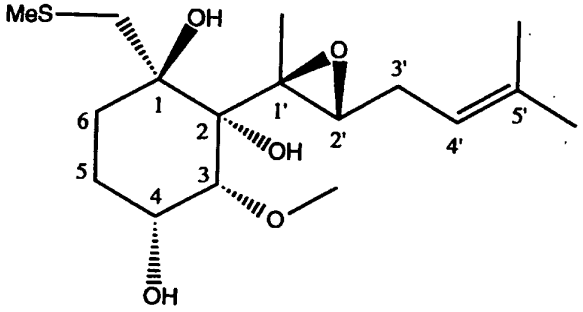
(8) an alkoxycarbonyl or phenoxycarbonyl group with or without a methylene or ethylene substituent, which can be optionally substituted.

7. A compound according to claim 6 wherein the formula is selected from the group consisting of:



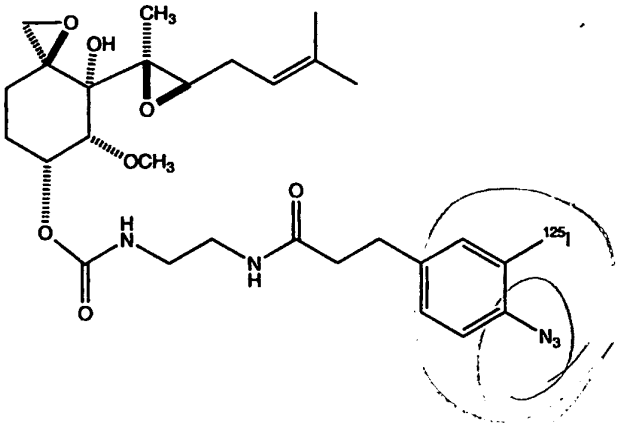
(5)

and



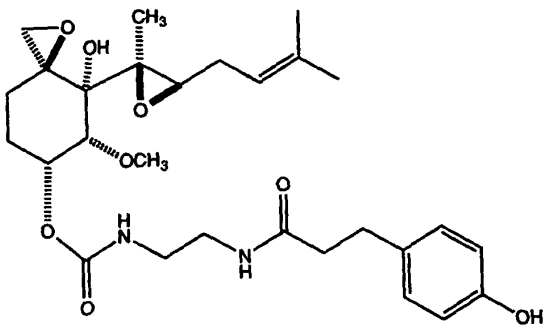
(6)

8. A compound having the formula selected from the group consisting of:



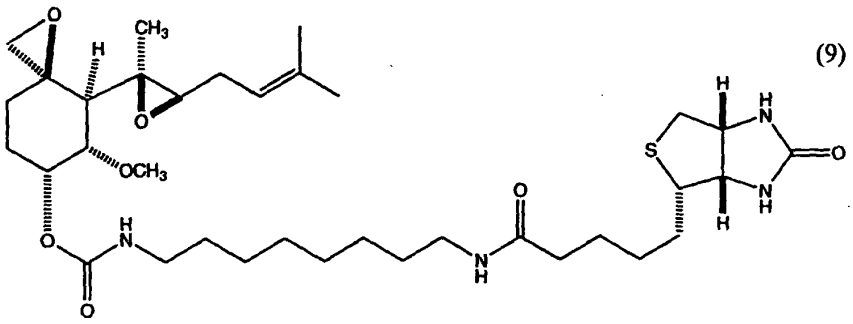
(7)

and



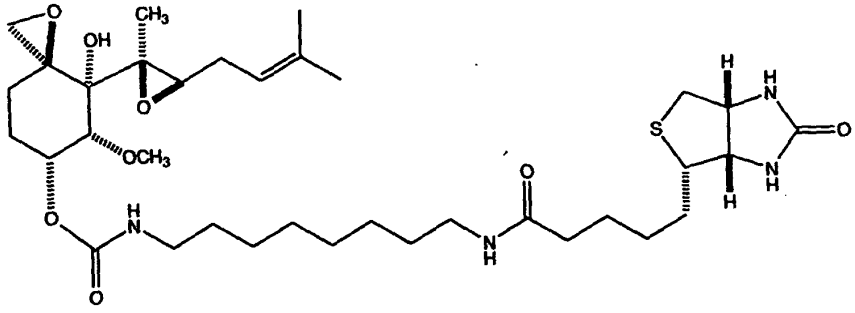
(8)

9. A compound having the formula selected from the group consisting of:



(9)

and



(10)

10. A method for determining if an animal is at risk for a disease involving abnormal angiogenesis or an immune reaction resulting in pathology, comprising:

providing an animal; and

evaluating an aspect of MetAP2 metabolism or structure in said animal, an abnormality in said aspect of MetAP2 metabolism or structure being diagnostic of being at risk for a disease involving abnormal angiogenesis or an immune reaction resulting in pathology.

11. The method of claim 10 wherein said disease is selected from the group consisting of tumors, diabetic retinopathy, inflammatory diseases, and arteriosclerosis.

12. The method of claim 10 wherein said pathology is selected from the group consisting of an autoimmune disease, an allergy, and a tissue graft rejection.

13. The method of claim 10 wherein said animal is a prenatal animal.

14. A method for identifying an agent that is anti-angiogenic or immunosuppressive, comprising:

providing MetAP2 polypeptide;

providing an agent;

contacting said agent with said MetAP2; and

evaluating the effect of said agent on an aspect of MetAP2 metabolism, a change in said aspect of MetAP2 metabolism being indicative of said agent being anti-angiogenic or immunosuppressive.

15. The method of claim 14 wherein said aspect of MetAP2 metabolism is an assay requiring said MetAP2.

16. The method of claim 15 wherein said assay is a methionine aminopeptidase assay.

17. The method of claim 14 wherein said agent is further tested for said agent's ability to inhibit cell proliferation, an inhibiting effect being indicative that said agent is anti-angiogenic.

18. The method of claim 17 wherein said cell proliferation is endothelial cell proliferation.

19. The method of claim 14 wherein said agent is further tested for said agent's immunosuppressive ability.

20. The method of claim 19 wherein said immunosuppressive ability is tested in a mixed lymphocyte reaction assay.

21. The method of claim 14 wherein said agent is an ovalicin analog, fumaginone or a fumaginone analog.

22. The method of claim 21 wherein said agent is a compound selected from the group consisting of formulas, I, II, III, IV and pharmaceutically acceptable salts thereof.

23. The method of claim 14 wherein said agent is selected from the group consisting of a MetAP2 polypeptide or a biologically active fragment or analog thereof, a nucleic acid encoding MetAP2 polypeptide or a biologically active fragment or analog thereof, and a nucleic acid encoding a MetAP2 regulatory sequence or a biologically active fragment or analog thereof.

24. The method of claim 14 wherein said agent is selected from the group consisting of a binding molecule for MetAP2 polypeptide or MetAP2 nucleic acid, and a mimetic of MetAP2 polypeptide or MetAP2 nucleic acid.

25. The method of claim 14 wherein said agent is selected from the group consisting of an antibody for MetAP2 or a binding molecule of MetAP2, and an antisense nucleic acid for MetAP2 or a binding molecule of MetAP2.

26. The method of claim 14 wherein said agent is selected from the group consisting of a natural ligand for MetAP2 and an artificial ligand for MetAP2.

27. The method of claim 14 wherein said agent is selected from the group consisting of an antagonist and an agonist.

28. The method of claim 14 wherein MetAP2 polypeptide is substantially pure.

29. The agent identified in claim 14.

30. A method for evaluating an agent for use in treating a disease involving abnormal angiogenesis or an immune reaction resulting in pathology, comprising:

providing a test cell, cell-free system or animal;

providing an agent;

administering said agent to said test cell, cell-free system or animal in a therapeutically effective amount; and

evaluating the effect of said agent on an aspect of MetAP2 metabolism, a change in said aspect of MetAP2 metabolism being indicative of the usefulness of said agent in treating a disease involving abnormal angiogenesis.

31. The method of claim 30 wherein said agent is an analog of ovalicin, fumaginone or a fumaginone analog.

32. The method of claim 30 wherein said agent is a compound selected from the group consisting of formulas I, II, III, IV and pharmaceutically acceptable salts thereof.

33. The method of claim 30 wherein said agent is selected from the group consisting of a MetAP2 polypeptide or a biologically active fragment or analog thereof, a nucleic acid encoding MetAP2 polypeptide or a biologically active fragment or analog thereof, and a nucleic acid encoding a MetAP2 regulatory sequence or a biologically active fragment or analog thereof.

34. The method of claim 30 wherein said agent is selected from the group consisting of a binding molecule for MetAP2 polypeptide or MetAP2 nucleic acid, and a mimetic of MetAP2 polypeptide or MetAP2 nucleic acid.

35. The method of claim 30 wherein said agent is selected from the group consisting of an antibody for MetAP2 or a binding molecule of MetAP2, and an antisense nucleic acid for MetAP2 or a binding molecule of MetAP2.

36. The method of claim 30 wherein said agent is selected from the group consisting of a natural ligand for MetAP2 and an artificial ligand for MetAP2.

37. The method of claim 30 wherein said agent is selected from the group consisting of an antagonist, an agonist and a super agonist.

38. The method of claim 30 wherein said agent is administered to a member selected from the group consisting of a transgenic cell and a transgenic animal.

39. The method of claim 30 wherein said agent is administered to said test cell or cell-free system in vitro, and if said change in said aspect of said MetAP2 metabolism occurs, then further administering said agent to a test animal in a therapeutically effective amount and evaluating the in vivo effect of said agent on an aspect of MetAP2 metabolism.

40. The agent identified in claim 30.

41. A method for evaluating a candidate anti-angiogenic or immunosuppressive agent for the ability to alter the binding of MetAP2 polypeptide to a binding molecule, comprising:

providing an agent;

providing MetAP2 polypeptide;

providing a binding molecule;

combining said agent, said MetAP2 polypeptide and said binding molecule; and

detecting the formation of a complex comprising said MetAP2 polypeptide and said binding molecule, an alteration in the formation of said complex in the presence of said agent as compared to in the absence of said agent being indicative of said agent altering the binding of said MetAP2 polypeptide to said binding molecule.

42. The method of claim 41 wherein the altering of the binding of said MetAP2 polypeptide to said binding molecule is inhibiting the binding.

43. The method of claim 41 wherein the altering of the binding of said MetAP2 polypeptide to said binding molecule is promoting the binding.

44. The agent identified in claim 41.

45. A method for evaluating a candidate anti-angiogenic or immunsuppressive agent for the ability to bind to MetAP2 polypeptide, comprising:

providing an agent;

providing a MetAP2 polypeptide;

contacting said agent with said MetAP2 polypeptide; and

evaluating the ability of said agent to bind to said MetAP2 polypeptide.

46. The agent identified in claim 45.

47. A method for evaluating a candidate anti-angiogenic or immunosuppressive agent for the ability to bind to a nucleic acid encoding a MetAP2 regulatory sequence, comprising:

providing an agent;

providing a nucleic acid encoding a MetAP2 regulatory sequence;

contacting said agent with said nucleic acid; and

evaluating the ability of said agent to bind to said nucleic acid.

48. The agent identified in claim 47.

49. A method for treating a cell having an abnormality in metabolism or structure of MetAP2, comprising:

providing a cell having an abnormality in metabolism or structure of MetAP2;

providing an agent selected from the group consisting of an ovalicin analog, fumaginone

or a fumaginone analog, said agent being capable of altering an aspect of MetAP2 metabolism or structure; and

administering said agent to said cell in a therapeutically effective amount such that treatment of said cell occurs.

50. The method of claim 49 wherein said cell is obtained from a cell culture or tissue culture.

51. The method of claim 49 wherein said cell is obtained from an embryo fibroblast.

52. The method of claim 49 wherein said cell is part of an animal.

53. The method of claim 52 wherein said animal is a non-human transgenic animal.

54. The method of claim 49 wherein said agent is a compound selected from the group consisting of formulas I, II, III, IV and pharmaceutically acceptable salts thereof.

55. The method of claim 49 wherein said agent is a compound selected from the group consisting of formulas 1, 2, 3, 4, 5, 6 and pharmaceutically acceptable salts thereof.

56. A method for treating abnormal angiogenesis in an animal, comprising:

providing an animal in need of treatment for abnormal angiogenesis;

providing an agent wherein said agent is an ovalicin analog, fumaginone or a fumaginone analog, said agent being capable of altering an aspect of MetAP2 metabolism or structure; and

administering said agent to said animal in a therapeutically effective amount such that treatment of said abnormal angiogenesis occurs.

57. The method of claim 56 wherein said agent is an ovalicin analog.

58. The method of claim 56 wherein said agent is fumaginone or a fumaginone analog.

59. The method of claim 56 wherein said agent is a compound selected from the group consisting of formulas I, II, III, IV and pharmaceutically acceptable salts thereof.

60. The method of claim 59 wherein said agent is a compound selected from the group consisting of formulas 1, 2, 3, 4, 5, 6 and pharmaceutically acceptable salts thereof.

61. A method for treating an animal at risk for abnormal angiogenesis, comprising:

providing an animal at risk for abnormal angiogenesis;

providing an agent wherein said agent is an ovalicin analog, fumaginone or a fumaginone analog, said agent being capable of altering an aspect of MetAP2 metabolism or structure; and

administering said agent to said animal in a therapeutically effective amount such that treatment of said animal occurs.

62. A method for treating a tumor in an animal, comprising:

providing an animal in need of treatment for a tumor;

providing an agent wherein said agent is an ovalicin analog, fumaginone or a fumaginone analog, said agent being capable of altering an aspect of MetAP2 metabolism or structure; and

administering said agent to said animal in a therapeutically effective amount such that treatment of said tumor occurs.

63. The method of claim 62 wherein said agent is an ovalicin analog.

64. The method of claim 62 wherein said agent is fumaginone or a fumaginone analog.

65. The method of claim 62 wherein said agent is a compound selected from the group consisting of formulas I, II, III, IV and pharmaceutically acceptable salts thereof.

66. The method of claim 65 wherein said agent is a compound selected from the group consisting of formulas 1, 2, 3, 4, 5, 6 and pharmaceutically acceptable salts thereof.

67. A method for treating an immune reaction which results in pathology in an animal, comprising:

providing an animal in need for treatment for an immune reaction which results in pathology;

providing an agent wherein said agent is an ovalicin analog, fumaginone or a fumaginone analog, said agent being capable of altering an aspect of MetAP2 metabolism or structure; and

administering said agent to said animal in a therapeutically effective amount such that treatment of said immune reaction occurs.

68. The method of claim 67 wherein said agent is an ovalicin analog.

69. The method of claim 68 wherein said agent is fumaginone or a fumaginone analog.

70. The method of claim 67 wherein said agent is a compound selected from the group consisting of formulas I, II, III, IV and pharmaceutically acceptable salts thereof.

71. The method of claim 70 wherein said agent is a compound selected from the group consisting of formulas 1, 2, 3, 4, 5, 6 and pharmaceutically acceptable salts thereof.

72. A method for treating an animal at risk for an immune reaction which results in pathology, comprising:

providing an animal in need for treatment for an immune reaction which results in pathology;

providing an agent wherein said agent is an ovalicin analog, fumaginone or a fumaginone analog, said agent being capable of altering an aspect of MetAP2 metabolism or structure; and

administering said agent to said animal in a therapeutically effective amount such that treatment of said animal occurs.

73. A pharmaceutical composition for treating abnormal angiogenesis in an animal,

comprising:

a therapeutically effective amount of an agent wherein said agent is an ovalicin analog, fumaginone or a fumaginone analog, said agent being capable of altering an aspect of MetAP2 metabolism or structure in said animal so as to result in treatment of said abnormal angiogenesis; and

a pharmaceutically acceptable carrier.

74. The method of claim 73 wherein said agent is an ovalicin analog.

75. The method of claim 73 wherein said agent is fumaginone or a fumaginone analog.

76. The method of claim 73 wherein said agent is a compound selected from the group consisting of formulas I, II, III, IV and pharmaceutically acceptable salts thereof.

77. The method of claim 76 wherein said agent is a compound selected from the group consisting of formulas 1, 2, 3, 4, 5, 6 and pharmaceutically acceptable salts thereof.

78. A pharmaceutical composition for treating an immune reaction which results in pathology in an animal, comprising:

a therapeutically effective amount of an agent wherein said agent is an ovalicin analog, fumaginone or a fumaginone analog, said agent being capable of altering an aspect of MetAP2 metabolism or structure in said animal so as to result in treatment of said immune reaction; and

a pharmaceutically acceptable carrier.

79. The method of claim 78 wherein said agent is an ovalicin analog.

80. The method of claim 78 wherein said agent is fumaginone or a fumaginone analog.

81. The method of claim 78 wherein said agent is a compound selected from the group consisting of formulas I, II, III, IV and pharmaceutically acceptable salts thereof.

82. The method of claim 78 wherein said agent is a compound selected from the group consisting of formulas 1, 2, 3, 4, 5, 6 and pharmaceutically acceptable salts thereof.

83. A phamaceutical composition for treating abnormal angiogenesis in an animal, comprising:

a therapeutically effective amount of an agent selected from the group consisting of a MetAP2 polypeptide or a biologically active fragment or analog thereof, a nucleic acid encoding MetAP2 polypeptide or a biologically active fragment or analog thereof, a nucleic acid encoding a MetAP2 regulatory sequence or a biologically active fragment or analog thereof, an antibody for MetAP2 and an antisense nucleic acid for MetAP2,

said agent being capable of altering an aspect of MetAP2 metabolism or structure in said animal so as to result in treatment of said abnormal angiogenesis; and

a pharmaceutically acceptable carrier.

84. A pharmaceutical composition for treating a tumor in an animal, comprising:

a therapeutically effective amount of an agent selected from the group consisting of a MetAP2 polypeptide or a biologically active fragment or analog thereof, a nucleic acid encoding MetAP2 polypeptide or a biologically active fragment or analog thereof, a nucleic acid encoding a MetAP2 regulatory sequence or a biologically active fragment or analog thereof, an antibody for MetAP2 and an antisense nucleic acid for MetAP2,

said agent being capable of altering an aspect of MetAP2 metabolism or structure in said animal so as to result in treatment of said tumor; and

a pharmaceutically acceptable carrier.

85. A pharmaceutical composition for treating an immune reaction which results in pathology in an animal, comprising:

a therapeutically effective amount of an agent selected from the group consisting of a

MetAP2 polypeptide or a biologically active fragment or analog thereof, a nucleic acid encoding MetAP2 polypeptide or a biologically active fragment or analog thereof, a nucleic acid encoding a MetAP2 regulatory sequence or a biologically active fragment or analog thereof, an antibody for MetAP2 and an antisense nucleic acid for MetAP2,

said agent being capable of altering an aspect of MetAP2 metabolism or structure in said animal so as to result in treatment of said immune reaction; and

a pharmaceutically acceptable carrier.

Fig. 1